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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JAGOE, DONNA A	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,548	SELLERS ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 56-65 are pending in this application.

Applicants' arguments filed November 5, 2007 have been fully considered and they are deemed to be persuasive regarding previous rejections of record. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

However, upon reconsideration, the following rejections and/or objections are newly applied. They constitute the complete set presently being applied to the instant application.

Terminal Disclaimer

The terminal disclaimer filed on November 6, 2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 09/214851 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 56-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the method of administration of nicotine to an individual. The step of administration of nicotine is considered critical because without administration of nicotine, inhibition of the metabolism of nicotine would not be possible. It is noted that conditions of the individual patient are selected from *inter alia* dependent tobacco use and non-dependent tobacco use, which may include administration of nicotine. Other members of the group, i.e. drug dependencies, psychosis, schizophrenia, Parkinson's disease, anxiety, depression and alcoholism do not require administration of nicotine and thus omit an essential step in the claim.

Claims 57-65 are indefinite to the extent that they read on the rejected base claim.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 56-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fernandez-Salguero et al., Gonzalez et al. WO 95/34679 A2 and Maenpaa et al. Biochem. Pharmacol. 1993 (U)

Fernandez-Salguero et al. teach CYP2A6 has the highest activity in the conversion of nicotine to cotinine (page 659, column 1, paragraph 3). Moreover, by using human liver microsomes, a correlation was found between coumarin 7-

hydroxylation, CYP2A6 protein content and oxidation of nicotine to its iminium ion, the intermediate en route to cotinine. This may have considerable importance in nicotine metabolism, which could lead to differences in smoking habits (page 659 column 2, 1st full paragraph). It was discovered that in some populations the CYP2A6 allele was not found and in these populations, the metabolism of coumarin was undetectable (see page 655, esp. column 2).

Gonzalez et al. teach CYP2A6 encodes a protein that metabolizes nicotine and coumarin and activates the tobacco-specific nitrosamine 4-(methylinitrosamino)-1-(3-pyridyl)-1-butanone) (NNK) (page 1, lines 26-30). Further, CYP2A6 has been associated with nicotine metabolism. Gonzalez et al. further disclose that nicotine, a component in tobacco, has several clinical uses, such as treatment of various neurological disorders such as Parkinson's disease and Alzheimer's disease. In addition, nicotine is used to treat tobacco addiction (page 11, lines 5-15).

Maenpaa et al. teach that coumarin is 7-hydroxylated by the P450 isoform CYP2A6 in humans and inhibitors of this CYP2A6 include furanocoumarin derivatives, methoxsalen (8-methoxypsoralen) and psoralen. The imidazole antimycotic miconazole were also potent non-specific inhibitors of coumarin 7-hydroxylase (COH) activity (see abstract).

Both Fernandez-Salguero et al. and Gonzalez et al. teach the importance of CYP2A6 in the metabolism of nicotine, and recognize that the absence of CYP2A6 would inhibit the breakdown of nicotine its iminium ion, and then to cotinine. It would have been obvious to one of ordinary skill in the art to administer an agent that is a

CYP2A6 inhibitor to regulate the metabolism of nicotine to cotinine, especially for the purpose of nicotine use disorders, as recognized by Fernandez-Salguero et al. who states that the regulation of nicotine metabolism may have considerable importance in nicotine metabolism, which could lead to differences in smoking habits (page 659 column 2, 1st full paragraph). The particular agents that inhibit the P450 isoform of CYP2A6 is well-known as demonstrated by Maenpaa et al. and

Regarding the administration of two or more CYP2A6 inhibitors, it is recognized that coumarin regulates the metabolism of nicotine to cotinine. As stated in In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

> It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art.

Regarding claim 58, wherein the liver enzyme function is inhibited by greater than 80%, as noted in *In re Best* (195 USPQ 430 (CCPA 1977)), and *In re Fitzgerald* (205 USPQ 594 (CCPA 1980)), the mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claims drawn to those things to distinguish over prior art. In such a situation, the burden is shifted to the applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; whether rejection is based on "inherency" under 35 U.S.C.

102, on "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, burden of proof is same. To quantify the level of inhibition of the liver enzyme function that was previously known to be inhibited by these agents as stated in the prior art is prima facie obvious.

Regarding the slow release formulation, modes of administration are art-recognized result-effective variables and it would have been obvious to one of ordinary skill in the art to optimize them from the teachings of the prior art.

Claims 56-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berkman et al. (W) in view of Seaton et al. (X) and Maenpaa et al. (U)

Berkman et al. teach that CYP2A6 is the primary enzyme that transforms (*S*)-nicotine to (*S*) nicotine $\Delta^{1'5'}$-iminium ion which is converted to (*S*) cotinine by the action of an exogenously added aldehyde oxidase (page 565, column 2, 2nd paragraph bridging to page 566, first paragraph). The formation of (*S*)-cotinine is strongly dependent on the previous drug administration history of each subject, and among the highest rates for (*S*)-cotinine formation at low concentration correlated well with immunoreactivity for cytochrome P450 2A6 (see abstract). The in vitro/in vivo correlation of the results suggests that the low amount of (*S*)-nicotine N-1'-oxygenation and the large amount of (*S*)-cotinine formed in human smokers are determined primarily by the kinetic properties of the human monooxygenase enzyme systems. It doesn't teach that the CYP2A6 enzyme enhanced inhibition of nicotine metabolism. It teaches that in the presence of CYP2A6, lots of (*S*)-cotinine was formed. Seaton et al. teach that there are many variables to the metabolism of nicotine in a human. It teaches that

Phenobarbital, an inducer of CYP450 enzymes induces not only metabolism of nicotine to cotinine, but also metabolism of cotinine to secondary metabolites (page 472 2nd paragraph). Conversely cimetidine, an agent that inhibits the CYP450 enzymes (page 472, 4th paragraph) decreased rates of nicotine metabolism so that twice as much nicotine was excreted unchanged in urine of Macaques (page 473 1st paragraph). Regarding the method for treatment of a condition requiring the regulation of nicotine metabolism to cotinine wherein the condition is dependent on tobacco use, Seaton et al. teach that chronic ethanol administration produces inductive effects of the CYP450 enzymes and induction of nicotine metabolism after chronic ethanol administration resulted in decreased plasma nicotine concentrations (increased metabolism) and might explain the increased urge to smoke cigarettes sometimes associated with heavy alcohol consumption. It would have been made obvious to one of ordinary skill in art at the time it was made to inhibit the CYP2A6 enzyme to inhibit metabolism of nicotine since Berkman et al. teach that CYP2A6 is the primary enzyme that transforms (*S*)-nicotine to (*S*) nicotine $\Delta^{1'5'}$-iminium ion which is converted to (*S*)-cotinine. It does not teach the specific agents that inhibit the CYP2A6 enzymes, however, Maenpaa et al. teach that coumarin is 7-hydroxylated by the P450 isoform CYP2A6 in humans and inhibitors of this CYP2A6 include furanocoumarin derivatives, methoxsalen (8-methoxypsoralen) and psoralen. The imidazole antimycotic miconazole were also potent non-specific inhibitors of coumarin 7-hydroxylase (COH) activity (see abstract).

Seaton et al. teaches inhibitors of CYP450 decrease nicotine metabolism (chronic ethanol administration) and agents that induce CYP450 increase nicotine

metabolism (Phenobarbital). Combined with the teaching of Berkman et al. that CYP2A6 is the primary enzyme that transforms (*S*)-nicotine to (*S*) nicotine $\Delta^{1'5'}$-iminium ion which is converted to (*S*) cotinine one would have been motivated to employ inhibitors of CYP2A6 to inhibit nicotine metabolism. Regarding claim 58, wherein the liver enzyme function is inhibited by greater than 80%, as noted in *In re Best* (195 USPQ 430 (CCPA 1977)), and *In re Fitzgerald* (205 USPQ 594 (CCPA 1980)), the mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claims drawn to those things to distinguish over prior art. In such a situation, the burden is shifted to the applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; whether rejection is based on "inherency" under 35 U.S.C. 102, on "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, burden of proof is same. To quantify the level of inhibition of the liver enzyme function that was previously known to be inhibited by these agents as stated in the prior art is prima facie obvious.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Response to Arguments

Applicant asserts that it would not be "obvious to choose from a finite number of possible enzymes that were suggested to be involved in the metabolism of nicotine to cotinine. It is unclear to the examiner what other enzymes are cited. As noted above, Fernandez-Salguero et al. teach CYP2A6 has the highest activity in the conversion of nicotine to cotinine (page 659, column 1, paragraph 3). Gonzalez et al. teach CYP2A6 encodes a protein that metabolizes nicotine and coumarin and activates the tobacco-specific nitrosamine 4-(methylinitrosamino)-1-(3-pyridyl)-1-butanone) (NNK) (page 1, lines 26-30). Further, CYP2A6 has been associated with nicotine metabolism. Berkman et al. teach that CYP2A6 is the primary enzyme that transforms (*S*)-nicotine to (*S*) nicotine $\Delta^{1'5'}$-iminium ion which is converted to (*S*)-cotinine. It is not clear to the Examiner what picking and choosing is needed in order to determine what enzyme is involved in the metabolism of nicotine to cotinine. As noted above, Fernandez-Salguero et al, Gonzalez et al. and Berkman et al. specifically point to that particular isoenzyme of CYP450. that inhibits metabolism of nicotine to cotinine and Maenpaa et al. specifically identify the agents instantly claimed as inhibitors of CYP2A6. There does not appear to be any difficulty in arriving at the decision of which enzyme to choose.

Applicants' reliance on the **post filing date** reference Draper et al. to allegedly provide evidence that cimetidine does not inhibit the CYP2A6 enzyme is not persuasive. The determination of obviousness or nonobviousness must be based upon what was known in the art at the time the invention was made. See 35 U.S.C. § 103: "A patent may not be obtained…if the differences between the subject matter sought to be

patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art".

Applicant states that the Examiner erred in the statement that Fernandez-Salguero teaches that CYP2A6 has the highest activity in the conversion of nicotine to cotinine because Fernandez-Salguero merely references another paper of this teaching. In response, it is not an error, unless the filing date of the reference that Fernandez-Salguero is quoting is after the filing date of the instant case. Applicant submits Cashman et al. and McCracken as proof that there is no teaching that CYP2A6 is a predictable solution for the inhibition of the metabolism of nicotine to cotinine in an individual In response, the Fernandez-Salguero reference clearly states that the discovery of CYP2A6 inhibitor is important in nicotine metabolism, which could lead to differences in smoking habits (page 659 column 2, 1st full paragraph).
Regarding the Berkman reference, applicant points to a table 1. Regarding the smoking habits of the subjects listed therein, it does not seem to be contained therein. Further, regarding formation of cotinine, Applicant does not seem to take into account the "drug history" listed on the chart. The variations are attributable to other drug use.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the degree of conversion of nicotine to cotinine in the liver) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988

F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicant has claims drawn to inhibition of liver enzyme function, not degree of metabolic clearance of nicotine to cotinine.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Seaton et al. teaches inhibitors of CYP450 decrease nicotine metabolism (chronic ethanol administration) and agents that induce CYP450 increase nicotine metabolism (Phenobarbital). Combined with the teaching of Berkman et al. that CYP2A6 is the primary enzyme that transforms (*S*)-nicotine to (*S*) nicotine $\Delta^{1'5'}$-iminium ion which is converted to (*S*) cotinine one would have been motivated to employ inhibitors of CYP2A6 to inhibit nicotine metabolism.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe
Examiner
Art Unit 1614

February 27, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614